

WHAT IS CLAIMED:

1. A therapeutic device for tissue regeneration comprising a biodegradable polymer that biodegrades to provide sustained release of an anti-inflammatory compound to a tissue.
- 5 2. The device of claim 1 wherein the anti-inflammatory compound is a salicylate.
3. The device of claim 1 wherein the anti-inflammatory compound is a non-steroidal anti-inflammatory compound.
- 10 4. The device of claim 1 wherein the anti-inflammatory compound is an aromatic anti-inflammatory compound.
5. The device of claim 1 wherein the anti-inflammatory compound is a cyclooxygenase inhibitor.
6. The device of claim 1 wherein the anti-inflammatory compound is a cyclooxygenase-1 inhibitor.
- 15 7. The device of claim 1 wherein the anti-inflammatory compound is a cyclooxygenase-2 inhibitor.
8. The device of claim 1 wherein the anti-inflammatory compound is etodolac, celebrex, meloxicam, piroxicam, nimesulide, nabumetone, rofecoxib or a combination thereof.
- 20 9. The device of claim 1 wherein the anti-inflammatory compound is aceclofenac, acemetacin, ϵ -acetamidocaproic acid, acetaminosalol, acetyl salicylic acid, alclofenac, alminoprofen, 3-amino-4-hydroxybutyric acid, amixetrine, ampiroxicam, amtolmetin guacil, apazone, aspirin, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, bermoprofen, α -bisabolol, bucolome, bucloxic acid, bufexamac, bumadizon, butibufen, calcium acetylsalicylate, carprofen, celebrex, choline salicylate, cinmetacin, clopirac, clidanac, diclofenac, difenamizole, difenpiramide, diflunisal, ditazol, droxicam, emorfazole, enfenamic acid, epirizole, etersalate, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, 25 fenoprofen, fentiazac, fepradinol, feprazole, flunoxaprofen, flurbiprofen,
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glucametacin, guaiazulene, ibufenac, ibuprofen, ibuproxam, imidazole
5 salicylate, indomethacin, indoprofen, isofezolac, isonixin, isoxepac,
isoxicam, ketoprofen, ketorolac, ketorolac tromethamine, lomoxicam,
lonazolac, loxoprofen, lysine acetylsalicylate, magnesium salicylate,
mefenamic acid, meloxicam, metiazinic acid, mofebutazone, mofezolac,
10 morazone, morpholine salicylate, nabumetone, 1-naphthyl salicylate,
naproxen, naproxen sodium, nimesulide, olsalazine, oxaceprol,
oxametacine, oxaprozin, oxyphenbutazone, paranyline, parsalmide,
perisoxal, phenyl acetylsalicylate phenylbutazone, phenyl salicylate,
15 piroxicam, piketoprofen, pipebuzone, pirazolac, piroxicam, pirprofen,
pranoprofen, proglumetacin, propyphenazone, proquazone, protizinic
acid, ramifenazone, rofecoxib, S-adenosylmethionine, salacetamide,
salsalate, salicylic acid, salicylsulfuric acid, sodium salicylate, sulindac,
superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap,
20 tenoxicam, terofenamate, thiazolinobutazone, tiaprofenic acid, tiaramide,
tinoridine, tolmetin sodium, tropsin, xenbucin, ximoprofen, zaltoprofen,
zileuton, zomepirac or a combination thereof.

10. The device of claim 1 wherein the tissue is neural, muscle, bone, tendon,
ligament or a combination thereof.
- 20 11. The device of claim 1 wherein the tissue is neural tissue.
12. The device of claim 1 wherein the biodegradable polymer comprises one or
more units of formula I:



I

wherein:

25 \mathbf{R}_1 is a group that will provide an anti-inflammatory agent
upon hydrolysis of polymer;
each A is independently an amide linkage, a thioester linkage, or an ester
linkage; and
L is a linking group.

13. The device of claim 1 wherein the biodegradable polymer comprises one or more units of formula II:



wherein:

5 \mathbf{R}_2 and \mathbf{R}_3 are each independently a group that will yield an anti-inflammatory agent upon hydrolysis of the polymer;

10 each A is independently an amide, thioester, or ester linkage; and

15 each L is independently a linking group.

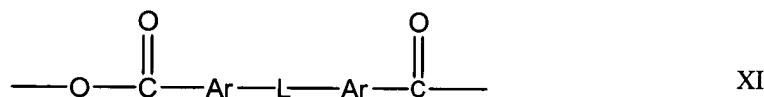
14. The device of claim 12 or 13 wherein the anti-inflammatory compound is a salicylate.

15. The device of claim 12 or 13 wherein the anti-inflammatory compound is aceclofenac, acemetacin, ϵ -acetamidocaproic acid, acetaminosalol, acetyl salicylic acid, alclofenac, alminoprofen, 3-amino-4-hydroxybutyric acid, amixetrine, ampiroxicam, amtolmetin guacil, apazone, aspirin, bendazac, benorylate, benoxaprofen, benzpiperylon, benzydamine, bermoprofen, α -bisabolol, bucolome, bucloxic acid, bufexamac, bumadizon, butibufen, calcium acetylsalicylate, carprofen, celebrex, choline salicylate, cinmetacin, clopirac, clidanac, diclofenac, difenamizole, difenpiramide, diflunisal, ditazol, droxicam, emorfazone, enfenamic acid, eprizole, etersalate, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fenoprofen, fentiazac, fepradinol, feprazone, flunoxaprofen, flurbiprofen, glucametacin, guaiazulene, ibufenac, ibuprofen, ibuproxam, imidazole salicylate, indomethacin, indoprofen, isofezolac, isonixin, isoxepac, isoxicam, ketoprofen, ketorolac, ketorolac tromethamine, lomoxicam, 20 ionazolac, loxoprofen, lysine acetylsalicylate, magnesium salicylate, mefenamic acid, meloxicam, metiazinic acid, mofebutazone, mofezolac, morazone, morpholine salicylate, nabumetone, 1-naphthyl salicylate, naproxen, naproxen sodium, nimesulide, olsalazine, oxaceprol, oxametacine, oxaprozin, oxyphenbutazone, paranyline, parsalmide, 25 perisoxal, phenyl acetylsalicylate phenylbutazone, phenyl salicylate,

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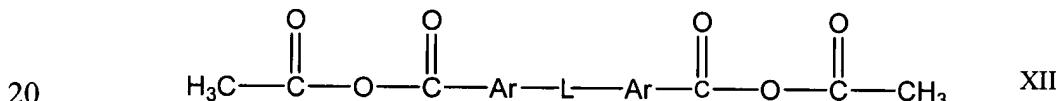
piroxicam, pikedoprofen, pipebuzone, pirazolac, piroxicam, pirprofen,
5 pranoprofen, proglumetacin, propyphenazone, proquazone, protizinic
acid, ramifenazone, rofecoxib, S-adenosylmethionine, salacetamide,
salsalate, salicylic acid, salicylsulfuric acid, sodium salicylate, sulindac,
superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap,
tenoxicam, terofenamate, thiazolinobutazone, tiaprofenic acid, tiaramide,
tinoridine, tolmetin sodium, tropesin, xenbucin, ximoprofen, zaltoprofen,
zileuton, zomepirac or a combination thereof.

10 16. The device of claim 1 wherein the biodegradable polymer comprises a
structure of formula XI:



15 wherein: Ar is a substituted or unsubstituted aromatic ring; and L is a
divalent, branched or unbranched, saturated or unsaturated, hydrocarbon
chain, having from 1 to 25 carbon atoms, wherein one to four of the carbon
atoms is optionally replaced by (-O-) or (-NR-).

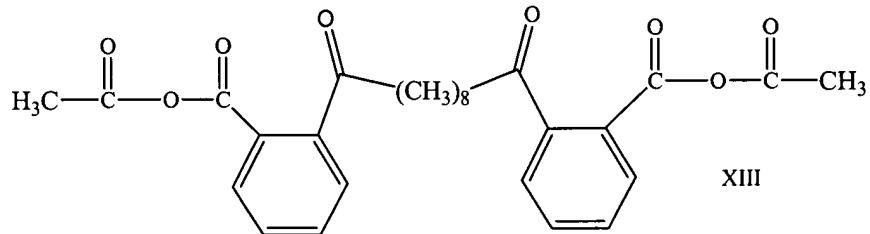
17. The device of claim 1 wherein the biodegradable polymer comprises a
dimeric anhydride of formula XII:



25 wherein: Ar is a substituted or unsubstituted aromatic ring; and L is a
divalent, branched or unbranched, saturated or unsaturated, hydrocarbon
chain, having from 1 to 25 carbon atoms, wherein one to four of the carbon
atoms is optionally replaced by (-O-) or (-NR-).

18. The device of claim 16 or 17 wherein Ar is phenyl or naphthyl.
19. The device of claim 16 or 17 wherein L is a divalent, saturated hydrocarbon
chain, having from 6 to 10 carbon atoms.

20. The device of claim 1 wherein the biodegradable polymer comprises a dimeric anhydride of formula XIII:



5 21. The device of claim 1 wherein biologically active molecules are stably adsorbed or covalently attached to the polymeric anti-inflammatory agent.

10 22. The device of claim 21 wherein the biologically active molecules comprise one or more polypeptides with an amino acid sequence comprising Arg-Gly-Asp, Tyr-Ile-Gly-Ser-Arg (SEQ ID NO:1), Ile-Lys-Val-Ala-Val (SEQ ID NO:2), SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13 or a combination thereof.

15 23. The device of claim 21 wherein the biologically active molecules comprise laminin, polylysine, fibronectin, collagen, polyethylene glycol, thrombospondin or a combination thereof.

20 24. The device of claim 21 wherein the biologically active molecules are adsorbed or covalently attached in a pattern on the polymeric anti-inflammatory agent.

25 25. The device of claim 24 wherein the pattern is designed to guide tissue regeneration along the pattern.

26. The device of claim 24 wherein the pattern is designed to guide neurite outgrowth.

27. The device of claim 24 wherein the pattern is a line, circle, oval, square, rectangle, diamond, triangle or a combination thereof.

28. The device of claim 24 wherein the pattern is up to 10,000 microns in width.

29. The device of claim 24 wherein the pattern is about 100 to 1000 microns in length.

30. The device of claim 24 wherein the pattern is comprised of lines.

31. The device of claim 30 wherein the line is about 1 to about 80 microns in 5 width and about 500 to about 1500 microns in length.

32. The device of claim 1 wherein the device can be implanted into a mammal at a site of neural injury.

33. A method for regenerating tissue comprising implanting a device into a 10 mammal wherein the device comprises a biodegradable polymer that biodegrades to provide sustained release of an anti-inflammatory compound to a tissue.

34. The method of claim 33 wherein the anti-inflammatory compound is a salicylate.

35. The method of claim 33 wherein the anti-inflammatory compound is a non- 15 steroidal anti-inflammatory compound.

36. The method of claim 33 wherein the anti-inflammatory compound is an aromatic anti-inflammatory compound.

37. The method of claim 33 wherein the anti-inflammatory compound is a cyclooxygenase inhibitor.

38. The method of claim 33 wherein the anti-inflammatory compound is a 20 cyclooxygenase-1 inhibitor.

39. The method of claim 33 wherein the anti-inflammatory compound is a cyclooxygenase-2 inhibitor.

40. The method of claim 33 wherein the anti-inflammatory compound is 25 etodolac, celebrex, meloxicam, piroxicam, nimesulide, nabumetone, rofecoxib or a combination thereof.

41. The method of claim 33 wherein the anti-inflammatory compound is 30 aceclofenac, acemetacin, ϵ -acetamidocaproic acid, acetaminosalol, acetyl salicylic acid, alclofenac, alminoprofen, 3-amino-4-hydroxybutyric acid, amixetrine, ampiroxicam, amtolmetin guacil, apazone, aspirin, bendazac,

benorylate, benoxaprofen, benzpiperylon, benzydamine, bermoprofen, α -bisabolol, bucolome, bucloxic acid, bufexamac, bumadizon, butibufen, calcium acetylsalicylate, carprofen, celebrex, choline salicylate, cinmetacin, clopirac, clidanac, diclofenac, difenamizole, difenpiramide, 5 diflunisal, ditazol, droxicam, emorfazone, enfenamic acid, epirizole, etersalate, etodolac, etofenamate, felbinac, fenbufen, fenclozic acid, fenoprofen, fentiazac, fepradinol, feprazone, flunoxaprofen, flurbiprofen, glucametacin, guaiazulene, ibufenac, ibuprofen, ibuproxam, imidazole 10 salicylate, indomethacin, indoprofen, isofezolac, isonixin, isoxepac, isoxicam, ketoprofen, ketorolac, ketorolac tromethamine, lomoxicam, lonazolac, loxoprofen, lysine acetylsalicylate, magnesium salicylate, mefenamic acid, meloxicam, metiazinic acid, mofebutazone, mofezolac, morazone, morpholine salicylate, nabumetone, 1-naphthyl salicylate, 15 naproxen, naproxen sodium, nimesulide, olsalazine, oxaceprol, oxametacine, oxaprozin, oxyphenbutazone, paranyline, parsalmide, perisoxal, phenyl acetylsalicylate phenylbutazone, phenyl salicylate, piroxicam, piketoprofen, pipebuzone, pirazolac, piroxicam, pirprofen, pranoprofen, proglumetacin, propyphenazone, proquazone, protizinic acid, ramifenazone, rofecoxib, S-adenosylmethionine, salacetamide, 20 salsalate, salicylic acid, salicylsulfuric acid, sodium salicylate, sulindac, superoxide dismutase, suprofen, suxibuzone, talniflumate, tenidap, tenoxicam, terofenamate, thiazolinobutazone, tiaprofenic acid, tiaramide, tinoridine, tolmetin sodium, tropesin, xenbucin, ximoprofen, zaltoprofen, zileuton, zomepirac or a combination thereof.

25 42. The method of claim 33 wherein the tissue is neural, muscle, bone, tendon, ligament or a combination thereof.

43. The method of claim 33 wherein the tissue is neural tissue.

44. The method of claim 33 wherein the pattern is designed to guide tissue regeneration along the pattern.

45. The method of claim 33 wherein the pattern is designed to guide neurite outgrowth.

46. The method of claim 33 wherein the biodegradable polymer comprises one or more units of formula I:

5



I

wherein:

R_1 is a group that will provide an anti-inflammatory agent upon hydrolysis of polymer;

each A is independently an amide linkage, a thioester linkage, or an ester linkage; and

10 L is a linking group.

47. The method of claim 33 wherein the biodegradable polymer comprises one or more units of formula II:

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wherein:

R_2 and R_3 are each independently a group that will yield an anti-inflammatory agent upon hydrolysis of the polymer;

each A is independently an amide, thioester, or ester linkage; and

each L is independently a linking group.

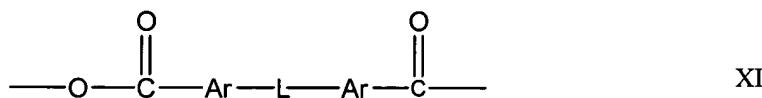
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48. The method of claim 46 or 47 wherein the anti-inflammatory compound is a salicylate.

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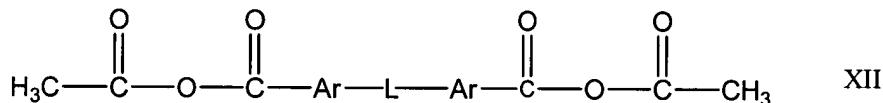
49. The method of claim 46 or 47 wherein the anti-inflammatory compound is aceclofenac, alminoprofen, 3-amino-4-hydroxybutyric acid, bromfenac, bumadizon, carprofen, 5-chlorosalicylic acid, diclofenac, diflunisal, ditazol, enfenamic acid, etodolac, fepradinol, flufenamic acid, glucametacin, meclofenamic acid, mefenamic acid, Niflumic acid, oxaceprol, S-adenosylmethionine, salsalate, tolfenamic acid, 5-trifluoromethylsalicylic acid, ximoprofen, zileuton or a combination thereof.

50. The method of claim 33 wherein the biodegradable polymer comprises a structure of formula XI:



5 wherein: Ar is a substituted or unsubstituted aromatic ring; and L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein one to four of the carbon atoms is optionally replaced by (-O-) or (-NR-).

10 51. The method of claim 33 wherein the biodegradable polymer comprises a dimeric anhydride of formula XII:

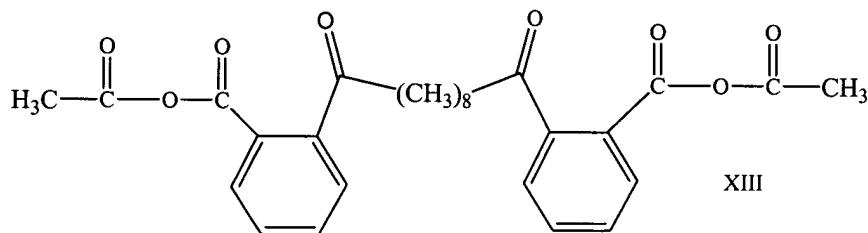


15 wherein: Ar is a substituted or unsubstituted aromatic ring; and L is a divalent, branched or unbranched, saturated or unsaturated, hydrocarbon chain, having from 1 to 25 carbon atoms, wherein one to four of the carbon atoms is optionally replaced by (-O-) or (-NR-).

52. The method of claim 50 or 51 wherein Ar is phenyl or naphthyl.

53. The method of claim 50 or 51 wherein L is a divalent, saturated hydrocarbon chain, having from 6 to 10 carbon atoms.

20 54. The method of claim 33 wherein the biodegradable polymer comprises a dimeric anhydride of formula XIII:



55. The method of claim 33 wherein biologically active molecules are stably adsorbed or covalently attached to the polymeric anti-inflammatory agent.

56. The method of claim 55 wherein the biologically active molecules comprise one or more polypeptides comprising Arg-Gly-Asp, SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, SEQ ID NO:9, SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13 or a combination thereof.

57. The method of claim 55 wherein the biologically active molecules comprise laminin, polylysine, fibronectin, collagen, polyethylene glycol, thrombospondin or a combination thereof.

10 58. The method of claim 55 wherein the biologically active molecules are adsorbed or covalently attached in a pattern on the polymeric anti-inflammatory agent.

15 59. The method of claim 58 wherein the pattern is designed to guide tissue regeneration along the pattern.

60. The method of claim 58 wherein the pattern is designed to guide neurite outgrowth.

20 61. The method of claim 58 wherein the pattern is a line, circle, oval, square, rectangle, diamond, triangle or a combination thereof.

62. The method of claim 58 wherein the pattern is up to 10,000 microns in length.

63. The method of claim 58 wherein the pattern is about 100 to 1000 microns in width.

25 64. The method of claim 58 wherein the pattern is comprises of lines.

65. The method of claim 64 wherein the lines are about 1 to about 80 microns in width and about 500 to about 1500 microns in length.

66. The method of claim 33 wherein the device is implanted into a mammal at a site of neural injury.